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EXAMINER	
KERR, KATHLEEN M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,226	ROSE ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *48 and 223* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on June 16, 2004), Applicants filed a response and election received on July 16, 2004. Claims 1-48 are pending in the instant Office action.

Election

2. Applicant's election of Group I, Claims 1-22, in the reply filed on July 16, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Applicant notes that the non-elected claims are being maintained for their reinstatement upon finding of an allowable product, presumably in view of *In re Ochiai*. However, the Examiner notes that the elected product, protein crystals, is neither used nor made by any of the methods in the pending claims. Thus, **all non-elected claims are NOT be subject to rejoinder** upon allowability of claims in the elected Group.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/234,879 and 60/263,458 filed on September 22, 2000 and January 23, 2001, respectively, as requested in the declaration.

Information Disclosure Statement

4. The information disclosure statement filed on August 23, 2002 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with the Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) In Figure 6, a DNA and protein sequence are disclosed without benefit of SEQ ID NOs.
b) In Figure 7, two protein sequences are disclosed without benefit of SEQ ID NOs.
c) On pages 25-26, peptides are disclosed without benefit of SEQ ID NO. Although residues numbers follow the disclosures, which SEQ ID NO they are relevant to is undisclosed. These same peptides appear in Claim 16 and, again, must be defined by SEQ ID NO.
d) Tables 1, 2, and 8, which contain atomic coordinates of mannosidase II, teach a linear polypeptide sequence that must be described by a SEQ ID NO, preferably in the description on pages 9-10.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

6. No statement that the paper copy of the sequence listing and the CRF copy of the sequence listing, both filed on January 15, 2002, are the same is made for the record. Such a statement is required.

Objections to the Drawings

7. Color photographs will be accepted if the conditions for accepting color drawings have been satisfied. A petition and fee requesting colored drawings for the instant application has been received (January 15, 2002). However, Applicant must comply with the below items (2) in bold for the instant objection to be withdrawn and the petition to be granted.

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 C.F.R. § 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 C.F.R. § 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, **an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification**:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Additionally, **black and white copies of the colored drawings, in which the details are clear, are required**; in particular, the labels of Figures 9A-9C and 11B and the overall quality of

Figures 3, 4, 9A-9C and 11B-11C are insufficient. See M.P.E.P. § 608.02 VIII and 37 C.F.R. § 1.84 for details about filing colored drawings in a utility application.

Applicant must either comply with the rules for submitting appropriate color drawings or delete the colors and make them of acceptable black and white quality, which would also require amendment to the specification wherein colors in the figures are referred.

Objections to the Specification

8. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Protein Crystals of a Mannosidase II Ligand-Binding Domain---

9. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species of the mannosidase for completeness.

10. In the specification, the Brief Description of the Drawings is objected to. Figure 6 is two pages and must be labeled as such (Figure 6A and Figure 6B); also, the description must include reference to Figure 6A and Figure 6B. The description must include reference to Figure 8A, Figure 8B, and Figure 8C. The description must include reference to Figure 9A, Figure 9B, and

Figure 9C. The description must include reference to Figure 10A, Figure 10B, and Figure 10C. The description must include reference to Figure 11A and Figure 11B.

11. The specification is objected to for the underlining on page 49 of a full paragraph that is inappropriate and unclear. Also unclear underlining is found in page 62.

12. The specification is objected to for inappropriate notation of an internet address. On page 17, lines 22-23, on page 35, line 26 and line 29, and page 582, lines 26, internet addresses are cited in an unacceptable form. See M.P.E.P. § 707.05(e) for the acceptable notation of an internet address.

13. The specification is objected to for the confusing inclusion of what appears to be a personal email address as a citation on page 20, lines 29. Clarification is required.

14. The specification is objected to for having unclear references as follows: Ducruix and Geige, 1992 (page 28, lines 17 and 23) is unclear without a book title. Otwinowski 1991 (page 28, lines 28-29) is unclear without a title. Furey, 1990 (page 29, line 7) is unclear.

15. The specification is objected to for being confusing with respect to the sequence listing. The sequence listing filed on January 15, 2002 discloses 9 sequences, none of which are mentioned in the specification by SEQ ID NO. Thus, the inclusion of these 9 sequences in the listing is confusing. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction is required.

Objections to the Claims

16. Claim 5 is objected to for being grammatically incorrect. In item (d), line 2, "provides" should be ---providing---. Correction is required.

17. Claim 8 is objected to for lacking a conjunction between items (a) and (b); insertion of an ---and--- is required.

18. Claims 10-11 and 16 are objected to for lacking a period at the end. Proper format is required.

19. Claim 11 is objected to for being grammatically incorrect. The "and" between His 90 and Asp 92 is inappropriate. Correction is required.

20. Claim 13 is objected to for being grammatically incorrect. The lack of an ---and--- between His 90 and His 471 is inappropriate. Correction is required.

21. Claim 16 is objected to for lacking a conjunction between items (d) and (e); insertion of an ---and--- is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 1-22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. The breadth of the term "crystal" in the instant claims is unclear. On pages 9-10, the term crystal is defined with an art-accepted meaning of "a three dimensional solid aggregate in which the plane faces intersect at definite angles and in which there is a regular structure of the constituent chemical species". However, the specification also continues on page 10 to include in the definition "a crystal structure derivable from the crystal ..., a 2D and/or 3D model based on the crystal structure, a representation thereof such as a schematic representation thereof or a diagrammatic representation thereof, or a data set thereof for a computer". These additional definitions of the term "crystal" are repugnant to the art-accepted meaning wherein a crystal means a protein crystal and not the protein's structure derived therefrom. While it is noted that Applicants may be their own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See M.P.E.P. § 7.34.02 and *In re* Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947).

The Examiner suggests deleting these repugnant definitions from the specification. The instant claims will be examined as if the term "crystal" is defined as only the art-accepted meaning as noted above; such a meaning is the only meaning indicated by the claim language to one of skill in the art. Clarification is required.

23. Claims 1, 6, and 9-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "mannosidase II ligand-binding domain" is unclear. On page 9 of the specification, Table 3 is described as showing "the ligand binding domain (active site) of a mannosidase II", and Table 3 actually lists "Interactions at an Active Site", not

mentioning a ligand binding site. It is unclear is the binding domain means the enzyme's active site or some other (perhaps overlapping) ligand binding site. Clarification is required.

24. Claims 4, 5, 8-14, and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims further characterize the claimed protein crystal by limiting it to having specific structures. However, all the references to structures are specific to the dGMII described in the instant application. In Claim 4, item (a), specific β-sheets as A, B and C in Figure 8B are required. Throughout the claims, specifically numbered residues are required. Thus, it is unclear if the crystal must be of dGMII or if it need only have general structures that correlate to those specifically described for dGMII in the claims.

Additionally, the numbering in Claims 4, 5, 8-14, and 16 is unclear since the exact structure (sequence) of the crystallized protein is unclear. On page 69 of the specification, numerous alterations of the 1108 amino acid protein of mannosidase II from *Drosophila* are referred to but are not clear. Thus, the numbering is unclear.

Clarification on these points is required.

25. Claim 7 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "the ligand" is unclear as the claim depends from Claim 3 and other claims, none of which refer to a ligand other than in the term "ligand binding domain" which refers to a region of the protein crystal and not the ligand itself. Perhaps Claim 7 should depend from Claim 6, which requires a ligand specifically. Clarification is required.

26. Claims 7 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derivative" of swainsonine is unclear. On page 12 of the specification, derivatives are described as being "known in the art", citing specific examples, but no metes and bounds of how different a compound can be and still be considered a swainsonine derivative is described. Clarification is required.

27. Claim 11 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "homologue" referring to particular amino acid residues present in the protein crystal is wholly unclear. Clarification is required.

28. Claim 20 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "cofactor" and "substrate" are extremely broad, but the implied meaning is that they are limited in the claim to cofactor(s) and substrate(s) of mannosidase II. Is this implied limitation a real limitation? If not, can any cofactor or any substrate be used? Such a genus is virtually unlimited. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

29. Claims 1, 6, and 9-18 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 is drawn to any protein crystal comprising a **mannosidase II** ligand-binding **domain**. Such a claim can be interpreted as requiring correlation with the binding site residues as shown in Table 3.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a protein crystal of mannosidase II (or more specifically, some portion of the 1108 amino acid sequence) from *Drosophila* is described in the atomic coordinates of the enzyme alone (Table 1), with swainsonine (Table 2) and with swainsonine, Zn^{2+}, Tris, and N-glycan (Table 8). These three species are not representative of the claimed genus because the genus only requires (at its most limited) residues correlating to the 128 residues of Table 3 (active/binding site residues). The genus encompasses a protein crystal of a

protein of approximately 1108 residues (length of mannosidase II from *Drosophila*) wherein only these 128 residues are defined while the remaining structure is wholly undefined. This undefined portion can include non-native amino acids and even other types of "residues", none of which are described. For these reasons, the instant claims lack adequate written description.

See also Case 5, Claim 1, of the Trilateral Project on protein 3D structure related claims at http://www.uspto.gov/web/tws/wm4/wm4_index.htm for additional reasoning.

30. Claims 1-18, 20, and 21 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to protein crystals of **mannosidase II** having **undefined structure**.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a protein crystal of mannosidase II (or more specifically, some portion of the 1108 amino acid sequence) from *Drosophila* is described in the atomic coordinates of the enzyme alone (Table 1), with swainsonine (Table 2) and with swainsonine, Zn^{2+}, Tris, and N-glycan (Table 8). These three crystals are not representative of the claimed genus because they lack a correlation of structure and function for the claimed genus. For each crystal, a specific sequence has been crystallized forming a specific crystal with particular unit cell coordinates and space group. Such structure describes claims to protein crystals adequately because the function is described (mannosidase) and the structure is described (sequence of protein and characteristics of crystal). However, the instant claims are drawn to crystal forms of any mannosidase of any sequence having any crystal structure except for, in some claims, the few particular limitations that define structural components (β-sheets, for example) and not overall structure as indicated by unit cell *and* space group of a crystal (a Claim like Claim 18 that also include the sequence crystallized, preferably by SEQ ID NO, and the space group would have adequate written description). For these reasons, the instant claims lack adequate written description.

Moreover, the specification does not teach even one representative species of a protein crystal of <u>*complete*</u> mannosidase II. Mannosidase II from *Drosophila* is a transmembrane protein with a short, cytoplasmic N-terminal tail, a transmembrane region, and a catalytic region (see van der Elsen *et al.*, 2001), and it is only this catalytic region (a truncated protein) that is

crystallized in the instant specification. Thus, Claims 2-6, 7, 8, 20, and 21 lack adequate written description.

See also Case 4 of the Trilateral Project on protein 3D structure related claims at http://www.uspto.gov/web/tws/wm4/wm4_index.htm. With respect to this Case 4, Protein P is noted as having a provided structure, which is distinct from the analysis of the instant claims wherein the structure is undefined.

31. Claim 17 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claim is drawn to a protein crystal with **$P2_1$ symmetry**.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

In the instant specification, crystals with $P2_12_12_1$ symmetry are described (see page 15). No example of crystals with $P2_1$ symmetry is described. Thus, no representative species of the claimed genus is disclosed with or without identifying characteristics. For these reasons, the instant claims lack adequate written description.

32. Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to protein crystals of mannosidase II containing a **mannosidase II inhibitor** wherein the inhibitor is described by what it does rather than what it is.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of any of the recited classes of possible antagonists, with or without identifying characteristics. Therefore, claim 16, as written, fails to satisfy the written description requirement.

A single species of mannosidase II inhibitor is taught as swainsonine. Crystal structures that include swainsonine bound to mannosidase II are also disclosed. Thus, any molecule fitting in the mannosidase II active site could be considered an inhibitor. However, such a genus is only described structurally. No correlation between such a structure and the function of inhibiting mannosidase II is described. Thus, the genus lacks adequate written description.

33. Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to protein crystals of mannosidase II from *Drosophila* as described by the atomic coordinates of Table 1, 2, and 8. To make such crystals would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches crystallization of a portion of mannosidase II from Drosophila under a variety of conditions, no specific crystallization conditions are pointed to as being the ones that produced the crystals whose atomic coordinates are in Tables 1, 2, and 8 (see pages 66-67). Moreover, the specific structure that was crystallized is not clearly described (see

for example, page 69). In the absence of specific structure (description of truncations, His-tags, glycosylation from recombinantly grown proteins, etc.) and crystallization conditions, one of skill in the art would be unable to make the claimed protein crystals.

"Protein crystals are difficult to grow" is a quote taken from a section title in Chapter 16 of the textbook Introduction to Protein Structure (Branden *et al.*). This section describes how the crystallization of proteins is usually quite difficult to achieve, the reasons for which include the screening of variable conditions of pH, temperature, protein concentration, solvent, precipitant, added ions, added ligands and others. The extensive screening procedures to try, using the many different combinations of the above conditions, are tedious and time-consuming. While the specification teaches some generic direction (some conditions and some sequence alterations to the 1108 amino acid protein), the specifics of crystallization of mannosidase II are not taught. However, these facts alone do not constitute an undue burden of experimentation placed on one skilled in the art to make or use the invention.

The specification provides some guidance and working examples (without details) for the production of a crystalline form of a portion of mannosidase II. The state of the prior art teaches the necessity of exact crystallization conditions for the duplication of research as evidenced in the careful accounting of said conditions as found in crystallization journal articles published throughout the prior art. The most crucial Wands factor in the instant case is the degree of unpredictability in obtaining the crystalline form of mannosidase II polypeptides in the absence of specific crystallization structure and conditions. A skilled artisan would be unable to reproduce the crystals, clearly produced by Applicants as evidenced by the atomic coordinates of Table 1, 2, and 8, without undue experimentation. Provided that Applicant can draw the

Examiner's attention to disclosure of specifically how to produce the claimed protein crystals (sequence crystallized, including how it was made [which is indicative of different structure, i.e., glycosylation, etc.] and crystallization conditions), the instant rejection as to the claims fully lacking enablement would be withdrawn.

With respect to Claims 1, 6, and 9-18, which are specifically drawn to crystals defined by the binding domain only (and not the entire structure), such claims further lack enablement for the full scope of the invention because the function (mannosidase) and spatial relationship are the only limitations on the claimed protein crystal. As described for Case 5, Claim 1 of the Trilateral Project on protein 3D structure related claims, a large number of species are encompassed having unspecified moieties with a very limited amount of structural restraint. "Because of the vast number of species encompassed by the claimed genus and the lack of guidance as to what structural changes may be made in the amino acid sequence between and around the active site residues such that the resulting polypeptide would retains the 3-dimensional structure and activity of the binding pocket, it would require undue experimentation to make and use the invention over the entire scope claimed" (see http://www.uspto.gov/web/tws/wm4/wm4_index.htm).

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

34. Claims 1-22 rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. To fulfill the utility requirement of 35 U.S.C. 101, an invention must have a

specific, substantial, and credible utility, which is disclosed in the specification, or which is well established as considered by one of ordinary skill in the art.

Claims 1-22 are drawn to protein crystals of mannosidase. While the specification is replete with examples of using the crystal to determine the atomic coordinates to determine the protein's structure for use in identifying inhibitors, etc., no use of the protein crystal itself is disclosed. To have utility under 35 U.S.C. § 101, the protein must have utility.

35. Claims 1-22 are also rejected under 35 U.S.C. § 112, first paragraph, enablement (how to use). Specifically, since the claimed invention is not supported by either an asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Additionally Cited Art

36. The following are cited to complete the record:

a) Ottensmeyer *et al.* (3D Reconstruction of Mannosidase II from Single particle Distributions: Noise Reduction Approached for Higher Resolution. Electron Microscopy (1998) 1:731-732) teach structures of mannosidase II; said structures are produced from single particles, not protein crystals.

b) Dole *et al.* (Crystallization and preliminary X-ray analysis of the class 1 alpha 1,2-mannosidase from *Saccharomyces* cerevisiae. J. Structural Biology (1997) 120(1): 69-72) teach crystallization of a different class of mannosidase.

c) Vallee *et al.* (Purification, crystallization and preliminary X-ray crystallographic analysis of recombinant murine Golgi mannosidase IA, a class I alpha-mannosidase involved in Asn-linked oligosaccharide maturation. (1999) 55 (Pt.2) 571-573) teach crystallization of a different class of mannosidase.

Conclusion

37. Claims 1-22 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Primary Examiner
Art Unit 1652

September 30, 2004